



FHL1 gene

four and a half LIM domains 1

Normal Function

The *FHL1* gene provides instructions for making three versions (isoforms) of a protein that plays an important role in muscles used for movement (skeletal muscles) and in the heart (cardiac muscle). The full-length isoform is known as FHL1A, or sometimes just FHL1. The other two isoforms, which are shorter, are called FHL1B and FHL1C.

FHL1A is the best-studied of the three FHL1 isoforms. Studies suggest that interactions between FHL1A and other proteins play a critical role in the assembly of sarcomeres, which are structures within muscle cells that are necessary for muscle tensing (contraction). These interactions also appear to be involved in chemical signaling within muscle cells, maintaining the structure of these cells, and influencing muscle growth and size.

Less is known about the FHL1B and FHL1C isoforms. FHL1B moves in and out of the nucleus and is also part of the nuclear envelope, which is a structure that surrounds the nucleus in cells. The protein's function in this structure is unknown. FHL1B and FHL1C are suspected to play roles in the normal structure and function of skeletal and cardiac muscles.

Health Conditions Related to Genetic Changes

Emery-Dreifuss muscular dystrophy

At least seven mutations in the *FHL1* gene have been found to cause Emery-Dreifuss muscular dystrophy. This condition affects skeletal and cardiac muscle, causing joint deformities called contractures, which restrict the movement of certain joints; muscle weakness and wasting that worsen over time; and heart problems, including an increased risk of sudden death.

Some of the *FHL1* gene mutations that cause Emery-Dreifuss muscular dystrophy change single protein building blocks (amino acids) in the FHL1 protein, while others insert or delete a small amount of DNA from the *FHL1* gene. All of the known mutations affect the FHL1A isoform. Depending on where the mutations occur, they may affect one or both of the other isoforms as well.

Studies suggest that mutations reduce the amount of functional FHL1 protein produced in cells or lead to the production of an abnormally short, nonfunctional version of the protein. A shortage of this protein disrupts the normal structure and function of cardiac and skeletal muscle cells. However, the exact mechanism by

which these changes cause joint contractures, muscle weakness and wasting, and heart problems remains unknown.

other disorders

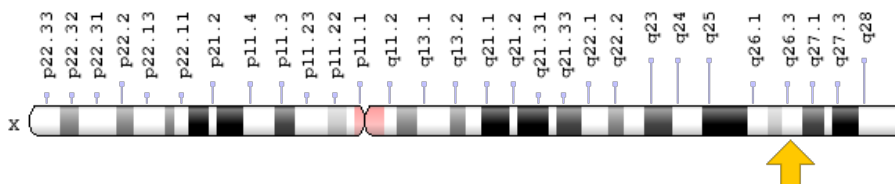
Several other muscle disorders also result from mutations in the *FHL1* gene. These include reducing body myopathy, X-linked scapuloperoneal myopathy, X-linked myopathy with postural muscle atrophy (XMPMA), and rigid spine syndrome. Together with Emery-Dreifuss muscular dystrophy, these conditions are known as *FHL1*-related myopathies or FHL1opathies. Features common among these disorders include skeletal muscle weakness, particularly in the shoulders and lower legs; contractures involving the joints of the spine (rigid spine); and heart abnormalities. However, the disorders differ in their age of onset, the severity of muscle weakness, and how quickly the signs and symptoms worsen.

More than 50 *FHL1* gene mutations have been associated with the *FHL1*-related myopathies. Each of these mutations affects some or all of the FHL1 isoforms. In general, mutations that affect all three isoforms cause more severe signs and symptoms than mutations that affect only one or two isoforms. Researchers have proposed several possible mechanisms by which *FHL1* mutations lead to the *FHL1*-related myopathies. In some cases, mutations lead to the production of a nonfunctional version of the protein or no protein at all. In others, mutations may result in the production of an abnormal version of the protein that can form clumps (called reducing bodies) within muscle cells. Reducing bodies have been found in people with reducing body myopathy, X-linked scapuloperoneal myopathy, and rigid spine syndrome, but it is unclear how they are related to the major features of these disorders.

Chromosomal Location

Cytogenetic Location: Xq26.3, which is the long (q) arm of the X chromosome at position 26.3

Molecular Location: base pairs 136,146,702 to 136,211,359 on the X chromosome (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- bA535K18.1
- FHL-1
- FHL1A
- FHL1B
- FLH1A
- four-and-a-half Lin11, Isl-1 and Mec-3 domains 1
- KYO-T
- KYOT
- LIM protein SLIMMER
- MGC111107
- RBMX1A
- RBMX1B
- skeletal muscle LIM-protein 1
- SLIM
- SLIM-1
- SLIM1
- SLIMMER
- XMPMA

Additional Information & Resources

Educational Resources

- Madame Curie Bioscience Database: LIM Domain and Its Binding to Target Proteins
<https://www.ncbi.nlm.nih.gov/books/NBK6372/>

GeneReviews

- Emery-Dreifuss Muscular Dystrophy
<https://www.ncbi.nlm.nih.gov/books/NBK1436>
- Myofibrillar Myopathy
<https://www.ncbi.nlm.nih.gov/books/NBK1499>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28FHL1%5BTI%5D%29+OR+%28four+and+a+half+LIM+domains+1%5BTI%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

OMIM

- FOUR-AND-A-HALF LIM DOMAINS 1
<http://omim.org/entry/300163>
- MYOPATHY, X-LINKED, WITH POSTURAL MUSCLE ATROPHY
<http://omim.org/entry/300696>
- REDUCING BODY MYOPATHY, X-LINKED 1A, SEVERE, WITH INFANTILE OR EARLY CHILDHOOD ONSET
<http://omim.org/entry/300717>
- REDUCING BODY MYOPATHY, X-LINKED 1B, WITH LATE CHILDHOOD OR ADULT ONSET
<http://omim.org/entry/300718>
- SCAPULOPERONEAL MYOPATHY, X-LINKED DOMINANT
<http://omim.org/entry/300695>

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
http://atlasgeneticsoncology.org/Genes/GC_FHL1.html
- ClinVar
<https://www.ncbi.nlm.nih.gov/clinvar?term=FHL1%5Bgene%5D>
- HGNC Gene Family: LIM domain containing
<http://www.genenames.org/cgi-bin/genefamilies/set/1218>
- HGNC Gene Symbol Report
http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=3702
- Leiden Open Variation Database: FHL1 Homepage
http://www.dmd.nl/nmdb/home.php?select_db=FHL1
- NCBI Gene
<https://www.ncbi.nlm.nih.gov/gene/2273>
- UniProt
<http://www.uniprot.org/uniprot/Q13642>

Sources for This Summary

- Bertrand AT, Bönnemann CG, Bonne G; FHL1 myopathy consortium.. 199th ENMC international workshop: FHL1 related myopathies, June 7-9, 2013, Naarden, The Netherlands. *Neuromuscul Disord.* 2014 May;24(5):453-62. doi: 10.1016/j.nmd.2014.02.002. Epub 2014 Feb 14.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/24613424>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5210188/>
- Cowling BS, Cottle DL, Wilding BR, D'Arcy CE, Mitchell CA, McGrath MJ. Four and a half LIM protein 1 gene mutations cause four distinct human myopathies: a comprehensive review of the clinical, histological and pathological features. *Neuromuscul Disord.* 2011 Apr;21(4):237-51. doi: 10.1016/j.nmd.2011.01.001. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/21310615>
- OMIM: FOUR-AND-A-HALF LIM DOMAINS 1
<http://omim.org/entry/300163>
- Gueneau L, Bertrand AT, Jais JP, Salih MA, Stojkovic T, Wehnert M, Hoeltzenbein M, Spuler S, Saitoh S, Verschueren A, Tranchant C, Beuvin M, Lacene E, Romero NB, Heath S, Zelenika D, Voit T, Eymard B, Ben Yaou R, Bonne G. Mutations of the FHL1 gene cause Emery-Dreifuss muscular dystrophy. *Am J Hum Genet.* 2009 Sep;85(3):338-53. doi: 10.1016/j.ajhg.2009.07.015. Epub 2009 Aug 27.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/19716112>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2771595/>
- Quinzii CM, Vu TH, Min KC, Tanji K, Barral S, Grewal RP, Kattah A, Camaño P, Otaegui D, Kunimatsu T, Blake DM, Wilhelmsen KC, Rowland LP, Hays AP, Bonilla E, Hirano M. X-linked dominant scapuloperoneal myopathy is due to a mutation in the gene encoding four-and-a-half-LIM protein 1. *Am J Hum Genet.* 2008 Jan;82(1):208-13. doi: 10.1016/j.ajhg.2007.09.013.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/18179901>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2253963/>
- Schessl J, Feldkirchner S, Kubny C, Schoser B. Reducing body myopathy and other FHL1-related muscular disorders. *Semin Pediatr Neurol.* 2011 Dec;18(4):257-63. doi: 10.1016/j.spen.2011.10.007. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/22172421>
- Schessl J, Taratuto AL, Sewry C, Battini R, Chin SS, Maiti B, Dubrovsky AL, Erro MG, Espada G, Robertella M, Saccoliti M, Olmos P, Bridges LR, Standring P, Hu Y, Zou Y, Swoboda KJ, Scavina M, Goebel HH, Mitchell CA, Flanigan KM, Muntoni F, Bönnemann CG. Clinical, histological and genetic characterization of reducing body myopathy caused by mutations in FHL1. *Brain.* 2009 Feb; 132(Pt 2):452-64. doi: 10.1093/brain/awn325. Epub 2009 Jan 29.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/19181672>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2724920/>
- Shalaby S, Hayashi YK, Goto K, Ogawa M, Nonaka I, Noguchi S, Nishino I. Rigid spine syndrome caused by a novel mutation in four-and-a-half LIM domain 1 gene (FHL1). *Neuromuscul Disord.* 2008 Dec;18(12):959-61. doi: 10.1016/j.nmd.2008.09.012. Epub 2008 Oct 25.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/18952429>
- Wilding BR, McGrath MJ, Bonne G, Mitchell CA. FHL1 mutants that cause clinically distinct human myopathies form protein aggregates and impair myoblast differentiation. *J Cell Sci.* 2014 May 15; 127(Pt 10):2269-81. doi: 10.1242/jcs.140905. Epub 2014 Mar 14.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/24634512>

- Windpassinger C, Schoser B, Straub V, Hochmeister S, Noor A, Lohberger B, Farra N, Petek E, Schwarzbraun T, Ofner L, Löscher WN, Wagner K, Lochmüller H, Vincent JB, Quasthoff S. An X-linked myopathy with postural muscle atrophy and generalized hypertrophy, termed XMPMA, is caused by mutations in FHL1. *Am J Hum Genet.* 2008 Jan;82(1):88-99. doi: 10.1016/j.ajhg.2007.09.004.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/18179888>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2253986/>
 - Ziat E, Mamchaoui K, Beuvin M, Nelson I, Azibani F, Spuler S, Bonne G, Bertrand AT. FHL1B Interacts with Lamin A/C and Emerin at the Nuclear Lamina and is Misregulated in Emery-Dreifuss Muscular Dystrophy. *J Neuromuscul Dis.* 2016 Nov 29;3(4):497-510.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/27911330>
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